Guidance for Industry

Good Laboratory Practice Regulations Management Briefings

Post Conference Report

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MANAGEMENT BRIEFINGS
ON THE GOOD LABORATORY PRACTICE REGULATIONS
POST CONFERENCE REPORT

On May 1, 2 and 3, 1979, FDA conducted half-day briefing sessions in Washington, Chicago and San Francisco on the Good Laboratory Practice Regulations. The purpose of the sessions was to provide the regulated industry with information to understand and comply with the regulations. The program included speakers from FDA as well as representatives from the American Association for Accreditation of Laboratory Animal Care (Dr. J. W. Ward), the National Association of Life Science Industries (Mr. D. P. Neilsen and Dr. H. C. Brown, Jr.), and the Society of Toxicology (Dr. R. B. Forney). Attendance at the three sessions was estimated at 800 persons affiliated with some 149-sponsor laboratories, 68 contractor laboratories, 19 university laboratories and 10 government laboratories. Some three hundred questions were posed; many of which were answered by the panelists during the question and answer portion of the sessions. At the sessions, the agency announced its intention to make available to the registrants and other interested persons a post conference report which would include the substance of all the answers to the questions posed at the conferences, including those questions which were not responded to because of time limitations.

INTRODUCTION

The questions received pertained to general and specific issues concerning the provisions of the GLPs, inspectional procedures, and FDA's enforcement policies. Many of the questions and their answers have been consolidated to eliminate redundancy and to focus more sharply on the issues.

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QUESTIONS AND ANSWERS

THE GLP REGULATIONS - GENERAL

1. Do the GLPs require the establishment of Technical Operation Manuals?

   No.

2. If a laboratory is accredited by AAALAC (American Association for Accreditation of Laboratory Animal Care), does this serve as assurance of meeting the GLP requirements for animal care and facilities?

   AAALAC accreditation does not substitute for Agency inspection nor does it guarantee automatic compliance with the applicable GLP sections. It is of value, however, in that it demonstrates that the facility has favorably passed a peer group review.

3. Results of the quality assurance unit inspections are not routinely available to an Agency investigator. However, the conforming amendments require that GLP deviations are to be reported in detail with each submission to the FDA. Are we required to send the contents of the quality assurance unit inspection report to the FDA?

   No. The GLP compliance statement in the conforming amendments to the GLPs was included for several reasons:

   (a) to provide an orderly transition across the effective date of the regulations. It was understood that applications for research and marketing permits submitted to the Agency for some period of time after the GLP effective date of June 20, 1979, would contain final reports of nonclinical studies begun and completed prior to the effective date, begun prior to the effective date and completed thereafter, and begun and completed after the effective date. Studies begun and completed prior to the effective date are not required to comply with the GLPs and accordingly, the conforming amendments require that differences be noted. Similar considerations apply to studies begun prior to and completed after the effective date, although in these studies, those portions underway as of the effective date are required to comply.

   (b) to provide for the submission of final reports of studies, which were not required to comply with the GLPs but which otherwise, contribute to safety evaluation. The GLPs do not apply to safety studies conducted by independent investigators studying regulated products. Such studies are not sponsored by the product manufacturer, nor is there any intention to submit the results to the Agency. The study results are published in the open literature. The sponsor is required red to submit the study to the Agency but could in no way control the research. If the

sponsor wishes to use the data in support of the application, the conforming amendments provide a mechanism by which the sponsor can prove that the study was not compromised. A similar situation exists for preliminary exploratory safety studies done by the sponsor.

(c) to foster GLP compliance attitudes by management. The conforming amendment causes management to act responsively to all cases of GLP non-compliance and to take prompt corrective actions.

With these purposes in mind, the conforming amendments require a brief statement of overall GLP compliance and need not contain the Quality Assurance Unit findings. The Quality Assurance Unit findings should cover short-term GLP deviations, which are promptly corrected. The conforming amendments statement should cover those systematic GLP deviations which have occurred throughout the study.

4. Who provides the GLP compliance statement required by the conforming amendments?

   This statement is provided by the applicant for the research or marketing permit.

5. What is the degree of compliance with GLPs, which the FDA will require for INDs submitted after June 20, 1979, but which include toxicology studies initiated before June 20, 1979, and completed after June 20, 1979?

   Those portions of the studies underway as of the effective date will have to be done in accord with the applicable provisions of the GLPs.

6. Do nonclinical laboratory studies completed *prior to June 20, 1979 but submitted as part of an IND or NDA subsequent to that date fall under the conforming amendments?

   These studies would not have to have been conducted under the GLPs but the conforming amendment statement of compliance is required.

7. How many members of the National Association of Life Science Industries (NALSI) come under the GLPs? How can the membership list be obtained?

   The Agency has not compiled such a list. A membership list is available from NALSI, 1747 Pennsylvania Avenue, NW, Suite 300, Washington, D.C. 20O06. All members who conduct nonclinical laboratory studies are subject to the GLPs.

8. Should a contract laboratory ask a sponsor if the article they are testing is subject to FDA regulations? Should these studies then be listed as a separate master list of studies to comply with the GLP regulations?

Contract laboratories should ask sponsors to identify studies which are associated with FDA regulated products, although the GLPs place this responsibility on the sponsor. A separate listing of such studies, apart from the firm's master list of all studies undertaken by the firm will satisfy the requirements of the GLPs.

9. What impact have the GLP regulations had on the cost of performing toxicology studies?

The president of a large contracting laboratory has stated that three years ago a chronic rat study could be done for about $80,000; and that the current cost is closer $250,000. He estimated that half of the increased cost is due to GLPs, 30% to larger numbers of test animals per study on present day protocols and 20% to inflation. The Agency has not developed cost estimates.

SUBPART A
GENERAL PROVISIONS

58.1 SCOPE
58.3 DEFINITIONSAPPLICABILITY TO STUDIES PERFORMED UNDER GRANTS AND CONTRACTS
58.15 INSPECTION OF A TESTING FACILITY

1. Are short-term microbiological screening tests and microbiological preservative stability research and development covered by the GLPs?

   Microbiological preservative stability research, development and quality control tests are not covered by the GLPs. However, microbiological tests conducted to establish the toxicological profile of an article are covered.

2. Does the Agency intend to audit analytical data collected on a test article?

   Yes, insofar as it contributes to the evaluation of a nonclinical laboratory study.

3. Does the Agency intend to audit draft final protocols and draft final reports?

   The regulations do not require that such materials be retained, however, if draft reports are available, they may be audited in order to help the Agency follow the process from raw data to final report.

4. Explain why the GLPs apply to "microorganisms or subparts thereof." How are microorganisms currently used by FDA in assessment of safety?

   For certain products, FDA does request that microbial tests be done for the purpose of obtaining information on potential neoplastic and mutagenic activity. Likewise, microsomal preparations (subparts thereof) are used as activating systems for certain in vitro tests. When this happens, the tests should be done in accord with the GLPs.

5. Do the GLPs apply to engineering/electronic testing laboratories that perform functionality tests on medical devices?

   No.

6. Is a licensed manufacturer of human biological products subject to continuing GLP inspection?

   The GLPs apply to safety studies submitted to the Agency in order to obtain the license. They do not apply to such studies conducted for the purpose of obtaining batch release of licensed biologicals.

7. Will nonclinical studies in support of medical devices which do not come in contact with man (e.g., stopcocks, a gas machine, a urine bag) be subject to the GLP regulations?

   If the medical device application for a research or marketing permit does not require the submission of safety data for approval, then the GLPs do not apply.

8. If a test article is produced by microbial fermentation, are tests run on the bacteria, such as pathogenicity or virulence covered by the GLPs?

   No.

9. Are studies performed for label purposes as required by the Federal Hazardous Substances Act considered to be nonclinical laboratory studies under the GLPs?

   No.

10. When an application for Premarket Approval for a Class III Device is scrutinized, would a GLP audit by FDA become a criterion for premarket approval?

    Safety data are required for Class III Devices and such data are to be collected under the GLPs, but an FDA audit will not automatically become part of the premarket approval mechanisms.

11. Are Class I, II and III Devices regulated products within the meaning of the GLPs?

    Yes.

12. Are data contained in a 510(k) notification subject to the GLPs?

    No.

13. How do the GLPs apply to the testing of electromechanical medical devices (non-animal work)?

    It is presumed that the question refers to engineering tests and in vitro tests of such devices conducted to assess functionality. In these cases, the GLPs do not apply.

14. Please elaborate on the preamble statement (43 FR 59989) that studies involving "diagnostic products" and "medical devices, which do not come in contact with or are implanted in man" are not within the scope of the GLPs.

    Failure of diagnostic products or medical devices, which do not come in contact with man or are not implanted does pose a safety hazard. This is also true for implantable devices. Tests to establish the reliability of these articles are functionality tests, not

safety tests. The GLPs cover implantable devices, which may cause adverse tissue reactions or may have components, which leach into the tissues and cause a toxic response.

15. Is an in vitro study to quantitate the amounts of residual proteolytic enzyme on a soft contact lens (the enzyme is used to clean the lens) a safety study which is covered by the GLPs?

    No, the enzyme is part of the lens manufacturing process and its analysis would be covered by the GMPs and not the GLPs. If, however, the proteolytic enzyme is sold as a means of cleaning lenses after purchase by a person, the enzyme is an accessory to a medical device and the safety studies supporting the use of the enzyme would be subject to the GLPs.

16. Do engineering laboratory tests done on components of implantable medical devices fall under the GLPs?

    No.

17. Are safety tests conducted on biological products exempt from the GLPs?

    Two kinds of safety tests are performed on human biological products. Those which are performed by the manufacturer prior to licensing, and those performed post licensing. The tests performed prior to licensing establish the basic safety profile of the product and they are covered by the GLPs. The safety tests performed post licensing are part of the required quality control assays, which permit the release of each batch of product. These tests are not covered by the GLPs. Safety testing of interstate biological products for use in animals is not covered by the GLPs since these products are not regulated by FDA.

18. Do the GLPs apply to veterinary drug and biological manufacturers even when the end products are strictly for veterinary use?

    The GLPs apply to animal drugs used on a prescription basis but they do not apply to interstate veterinary biologicals since these products are regulated by USDA. Intrastate veterinary biologicals, which are considered to be new animal drugs, are also covered by the GLPs.

19. If an organization has separate divisions for basic research and for toxicological safety testing, will the basic research division be subject to inspection under the GLPs?

    No, as long as the basic research division is not providing any service function for the safety-testing unit.

20. Do the GLP requirements apply to an equal degree to acute, medium-term, and long-term studies?

    The GLPs apply equally to all nonclinical laboratory studies. It should be recognized, however, that short-term (less than 6 months) studies need not be inspected as frequently as long term (more than 6 months) studies by the quality assurance unit.

21. Are preliminary protocol development or design studies that employ laboratory animals covered by the GLPs?

    No, these are preliminary exploratory studies.

22. If an acute oral toxicity study, a 90-day oral toxicity study, and a two-year chronic study are done, is only the two-year study required to be done under the GLPs?

    No. Each study, regardless of its duration or complexity should be considered in terms of its purpose. A study, which is conducted for the purpose of estimating the safety of a product in, humans or animals and which will be submitted to FDA, is covered under the GLPs. This includes acute oral toxicity studies as well as 90-day oral toxicity studies and two-year chronic studies. In early phases of research, acute studies are often used to select the most promising product from a group of candidate products. In this sense acute studies are exploratory or screening in nature and would be exempted from the GLPs. There are also special situations where a 90-day oral toxicity study or even a chronic oral toxicity study may be exempted from GLPs. For example, a multinational company may want to develop Product A for a very specific foreign market. The company has no intention of ever applying to FDA for an investigational or marketing permit for Product A. Long-term safety studies with Product A for the purpose of foreign registration would be exempted from GLPs.

23. Will you please ease define a range-finding study and will such studies be inspected?

    A range-finding study is conducted to gather information such as dose range or toxicological end point to permit the more proper design of a subsequent nonclinical laboratory study. Such studies, which are usually short-term, are preliminary exploratory studies, which are exempt from the GLPs if properly labeled as "range-finding" or "preliminary pilot study" or similar designation. These studies will usually not serve as the basis of inspection, but may be reviewed to determine whether the operation of a facility is in compliance with the GLPs. Although the studies are exempt from the GLPs, they must still be submitted to the Agency as part of the respective application for a research or marketing permit.

24. Does the Agency agree that the GLPs are applicable to safety studies intended for submission to the Agency in support of the approval of a regulated product and that

they are not applicable to preliminary exploratory studies, screening studies, and range-finding studies whose purpose is to develop or improve the experimental design of a planned nonclinical laboratory study?

Yes.

25. Many toxicological studies are conducted on products or formulations, which are comprised entirely of materials which are known to be safe. Such studies are intended to be a quality control measure to determine lack of product integrity or to detect adulteration. Do the GLPs apply to such studies?

    No. The Agency considers such studies to be quality control studies, which are not subject to the GLPs.

26. Does a food manufacturer's laboratory, which conducts only microbiological screening studies, have to comply with the GLPs?

    Generally no. The GLPs apply to safety studies intended for submission to the Agency in support of product approval. Food microbiology studies are quality control studies not subject to the regulations.

27. Do the GLPs apply to laboratories, which perform routine sterility analyses on marketable medical devices, which have been treated with gas for the purpose of sterilization?

    No.

28. Are studies of approved drugs or devices undertaken for physician education, advertising or pharmaceutical marketing purposes subject to the GLPs?

    No.

29. Do the GLPs apply to safety substantiation studies conducted on over-the-counter drugs, which are covered by a final monograph?

    No.

30. It is not clear whether a laboratory involved solely in chemical analysis support of a nonclinical laboratory study would be required to comply with the GLPs. Can this be clarified?

    Yes. Analytical laboratories must comply with the GLPs to the extent that they provide data, which support the nonclinical laboratory study. Only those portions of the laboratory, those procedures and those personnel involved are required to be in compliance with the GLPs.

31. What is FDA's position regarding the testing of "medical foods" according to GLP requirements?

    By "medical foods," it is assumed that you mean either diets, which complement human therapy, or dietary products used for nutritional purposes. Such products usually do not require an application for a research or marketing permit and therefore they do not fall under the scope of the GLPs. If an application is required, the safety tests would be within the scope.

32. How do previous GLP inspections prior to these new regulations affect our being accredited by AAALAC?

    Not at all. AAALAC accreditation deals with animal care practices and is a process, which is independent from FDA's GLP inspections.

33. What about the special problems university laboratories have with complying to the GLPs? Are these laboratories expected to comply to the same degree as industry laboratories?

    In crafting the final order, the Agency was cognizant of the problems of university laboratories and certain changes were made which would simplify compliance for all laboratories without frustrating the intent of the GLPs. All laboratories are expected to comply to the same degree since product safety decisions are of equal importance regardless of the size or of the organizational structure of the laboratory doing the study.

34. Are analytical laboratories, which perform support characterization of a substance subject to GLP inspection? If so when and under what circumstances?

    Yes, the laboratories are subject to inspection at the request of the headquarters bureau, which is evaluating the nonclinical laboratory studies on that substance. The kind of inspection will be a data audit which will include only those records, personnel and portions of the laboratory which collected the data on that substance.

35. Does the definition of nonclinical laboratory study include electrical safety of medical devices or evaluation of "safe" operation of equipment, i.e., fail-safe studies for a critical device?

    No, functionality studies do not fall within the scope of the GLPs.

36. Do metabolism studies come under the scope of the GLPs?

    For drugs and feed additives used in food producing animals, metabolism studies come under the GLPs. In these cases, the studies are intended to define the tissue

residues of toxicological concern as well as to estimate tissue depletion. Such studies on other regulated products are usually conducted as part of the pharmacological evaluation and would not be covered. However, metabolism studies on food additives are covered.

37. Does the FDA have a list of laboratories, which do and do not comply with the GLPs?

    No, but the Agency maintains a list of the laboratories which have been inspected. Copies of individual inspection reports may be obtained as a Freedom of Information request.

38. Does the term "nonclinical laboratory study" include animal laboratory studies, which are designed for the explicit purpose of determining whether a test article has reasonable promise of clinical effectiveness, and in which observations bearing on clinical safety are only incidental or fragmentary, or at most, clearly secondary?

    No.

39. With regard to the Submission of foreign toxicity data to the Agency, must a sponsor monitor and inspect the foreign laboratories and audit the final study report?

    Not necessarily. The foreign laboratory would be considered a contract laboratory and the sponsor's responsibilities would be as set forth in question 40 (below).

40. If a sponsor company utilizes a contract laboratory, who is responsible for the GLP compliance of the contract laboratory? Should a sponsor have its own quality assurance unit to monitor contracted studies? If a contract laboratory has its own quality assurance unit, is it necessary for the sponsor to audit these studies also? How does a sponsor validate a report of a study performed at a contract lab?

    The ultimate responsibility for assuring the quality and integrity of a nonclinical laboratory study rests with the person (sponsor) who submits the application for a research or marketing permit to the Agency. This responsibility can be discharged as follows:

    Case 1. The contract laboratory has a fully functional quality assurance unit and is operating in conformance with the GLPs. In this case, the sponsor should assure itself that the contract facility has adequate personnel, facilities, equipment and standard operating procedures to perform the study properly. Likewise, the sponsor should examine the procedures used by the contract facility's quality assurance unit and make a determination that such procedures are adequate to obtain GLP compliance. Finally, the sponsor should review the final report (not audit since this has already been done by the contract facility) for consistency and accuracy.

Case II. The contract laboratory does not have a quality assurance unit and may or may not be operating in conformance with the other provisions of the GLPs. In this case, the sponsor must perform all quality assurance functions and take whatever steps are required to promote the GLP compliance of the contract facility. The final report will have to be audited since this has not been done by the contractor.

SUBPART B
ORGANIZATION AND PERSONNEL

58.29 PERSONNEL
58.31 TESTING FACILITY MANAGEMENT
58.33 STUDY DIRECTOR
58.35 QUALITY ASSURANCE UNIT

1. Must an employee with a cold or the flu be removed from the study?

   This decision is left to management. If an employee's disease can adversely affect the test system or the study results, the employee should be removed from the study until the employee is well.

2. In view of the precautions being taken to adequately document diet preparation, the provision for quality assurance unit inspection of the procedure more than once on each study, what is the Agency's thinking on what is to be accomplished by retaining all samples for the period required?

   Maintaining a reserve sample is necessary to provide independent assurance that the test system was exposed to the test article as specified in the protocol. If the results of the study raise questions about the composition of the test article, the reserve sample analysis may provide answers to the questions. The Agency is willing to accept a petition from industry to consider changing the reserve sample retention provisions as discussed elsewhere.

3. Under what circumstances may QAU audit reports be inspected by FDA? Is there any requirement to maintain these reports or can they be discarded?

   QAU audit reports as a matter of administrative policy are exempt from routine FDA inspection. FDA's access to QAU audit reports would be through the Courts should the subject matter of those reports be litigated. Since there is no FDA requirement that these reports be maintained, the disposition of these reports is up to the firm's management. FDA advises that such records not be destroyed without the firm seeking advice from its legal counsel.

4. What are the quality assurance unit inspection requirements for acute and short-term studies?

   For studies lasting less than 4 weeks, each final report should be reviewed by the quality assurance unit for accuracy. With regard to the in process phases (dose preparation, dose administration, in vivo observation and measurement, necropsy, etc.), a random sampling approach could be used so that over a series of studies each critical phase has been monitored. The random sampling approach should be

statistically designed so that it is adequate for revealing GLP deviations. The approach and its justification should be made a part of the standard operating procedures of the quality assurance unit.

5. What constitutes proper quality assurance unit inspection of each phase of a nonclinical laboratory study?

   A variety of procedures are acceptable for performing a quality assurance unit inspection. The GLPs do not mandate specific procedures. The development of an acceptable procedure should not necessarily be limited to but should consider the following:

   (a) nonclinical laboratory studies lasting longer than 6 months should be inspected every 3 months; whereas, studies lasting less than 6 months should be inspected at suitable intervals,

   (b) each phase of the study should be inspected,

   (c) inspection reports are to be submitted to management and to the study director, and

   (d) the purpose of the inspections is to identify significant problems, which may affect study integrity, and to determine that no changes from approved protocols or standard operating procedures were made without proper authorization.

   The phases of a particular study will be determined by the nature of the study. For example, the phases of a typical feeding study include the following:

   1. protocol development and approval
   2. test article characterization
   3. test article stability determination
   4. test article-carrier mixture preparation
   5. test article-carrier mixture sampling
   6. test article-carrier mixture homogeneity determination
   7. test system quarantine
   8. test system allocation to housing
   9. test article carrier mixture distribution to test system
   10. periodic measurements
       - animal observations
       - food consumption
       - body weights
       - blood sampling -- hematology and clinical chemistry
   11. necropsy -- histopathology
   12. statistical analyses and report preparation

The type of inspection will depend on the nature of the phase. Each phase must be inspected at least once during the study; the times selected for inspection should be those most likely to reveal problems before the quality of the data generated could be adversely affected.

6. Could you take a typical subacute 14-day study and define the phases?

   Phases in a short term study (depending on the type) would include protocol preparation, dose preparation, animal allocation, test system dosage, animal observation, necropsy, data recording, data analysis and final report writing.

7. By what authority may the Agency examine master schedule sheets for studies, which may never be used in support of an application for a research or marketing permit?

   Studies that are not intended to be used to support an application for a research or marketing permit are not covered by the GLPs and need not appear on the master schedule sheet. If however, the studies are intended to be submitted, then they should be listed and can be inspected by the Agency under its authority to evaluate the results of studies designed to demonstrate product safety.

8. Are acute studies to be included on the master schedule sheet?

   Yes, if they fall within the scope of the GLPs.

9. In regard to the master schedule sheet, can the "current status of each study" be satisfied by listing the starting date and completion date of the study? Can the "status of the final report" be satisfied by listing the estimated or actual date of issuance of the final report?

   Although the GLPs do not specify entries for "current status of each study," dates alone would not be adequate. Suggested entries that are possible include "study proceeding according to protocol," "study proceeding according to protocol as amended on such-and-such date," "study terminated due to such-and-such," etc. Likewise, entries for the status of the final report might include "awaiting final hematology report," "data in statistical analysis," "first draft prepared," "draft under circulation for review and comment," etc.

10. In our laboratory, critical operations for all studies are carried out by the same individuals using essentially similar procedures. Would it be adequate for the quality assurance unit to inspect a set of representative operations for GLP and standard operating procedure compliance that would incorporate a good cross-section of studies?

    No, but refer to the answer under question 4 above.

11. In reference to the quality assurance unit review of the final report, you have indicated that not all numbers have to be traced. Do you have in mind a standard, which describes an acceptable level of accuracy, e.g., 90%, 99%, 99.9%, 99.99%?

    The quality assurance unit review is to ensure that the final report accurately reflects the raw data. Inasmuch as final reports of certain long-term studies can encompass several hundred thousand observations, it would be a prodigious exercise for the quality assurance unit to verify and trace all raw data. Further, the Agency did not mean to require that the quality assurance unit review would include a check of the accuracy of the calculations used to arrive at the final report. This activity would be redundant since the contributing scientists would have already done so in preparing their reports. Rather, the review was expected to be of sufficient depth to reveal inaccuracies in the final report. Consequently, the Agency envisioned the development of a statistically based system, whereby; a random sample of the results in the final report is traced. The procedure should be made a part of the standard operating procedures.

    The Agency has not established an acceptable level of accuracy of the trace.

12. Is the master schedule sheet intended to be prospective or historical? If it is historical, what is the required retention period?

    The master schedule sheet is intended to include a listing of all nonclinical laboratory studies currently in progress as well as those which have been conducted during the terms specified in section 58.195 of the GLPs.

13. Does the master schedule sheet have to list studies on compounds for which no data has yet been submitted to the Agency?

    Yes. The GLPs cover all nonclinical laboratory studies of Agency regulated products that support or are intended to support applications for research or marketing permits.

14. The GLPs state that the quality assurance unit should assure that the final report reflects the study results. Is it required that every final report be reviewed by the quality assurance unit?

    Yes. This procedure helps to ensure the accuracy of the final report.

15. Does the quality assurance unit review of each final study report have to be reported to management?

    Yes. The quality assurance unit must make periodic reports to management and the study director on each study. These reports should include the results of the final report review.

16. At our facility the quality assurance unit reports directly to the executive vice president of the company and not to the vice president of research and development. Is it necessary for us to formulate a separate quality assurance unit within the research and development department?

    The GLPs require that the quality assurance unit director and the study director cannot be the same person. The quality assurance unit must report to a level of management that has the authority to effect the corrective action as indicated by the quality assurance unit inspection reports. How this is accomplished organizationally is a management prerogative.

17. Is it acceptable for the quality assurance unit to report to the management person who is also responsible for drug safety evaluation?

    This is acceptable provided that the management person is not the study director for the studies being inspected by the quality assurance unit.

18. Is it permissible to have a pharmacologist in the research division serve as the director of the quality assurance unit?

    The GLPs state that a person may not perform both quality assurance functions and study direction and conduct functions for the same study. Thus, a pharmacologist in a research division could serve as the director of the quality assurance unit as long as he or she did not otherwise participate in the studies under review by the quality assurance unit.

19. How is the requirement for a quality assurance unit to be interpreted when the testing facility is itself a quality assurance unit?

    By definition, a testing facility could not be a quality assurance unit. A quality assurance unit, which conducts nonclinical laboratory studies, should make separate provision for the performance of the GLP quality assurance functions.

20. Is a member of the statistical department of a testing facility entitled to be a member of the quality assurance unit?

    This decision rests with facility management but such a choice is acceptable.

21. Company A is conducting a study. Company B performs animal work for Company A to the extent of implanting test material, recovering test materials and tissues, and returning these to Company A for analysis and conclusions. Which company is designated as the testing facility, which company designates the study director, and which company does the study director work for?

In the cited example, Company A would be the study sponsor while Company B would be a contract laboratory performing a portion of a nonclinical laboratory study. Both companies would be considered testing facilities, but, since the GLPs require a single study director for each study, Company A would designate the study director. Company B would, no doubt, designate a participating scientist in charge of the animal work and would have the responsibility of submitting a participating scientist's report to Company A for inclusion into the final report.

22. Is it acceptable to have two study directors for a single study at the same time?

    No. The regulations require a single point of study control, which has been vested in the study director.

23. Do the GLPs permit the designation of a "deputy" or "acting" study director to be in charge of a nonclinical laboratory study when the study director is out of town, on vacation, etc.?

    Yes.

24. Must the study director personally verify all observations made during a nonclinical laboratory study?

    No. The study director must assure that study procedures are adequate to ensure the collection of valid data.

25. A study is only as good as the people who perform it and most importantly as the person who directs it. What does the Agency do to assess the training and experience of toxicologists?

    The assessment of the training and experience of personnel is a routine part of the GLP Compliance Program. Agency investigators collect summaries of training and experience for individuals participating in the study. These summaries are evaluated by the headquarters scientific review staff.

26. In view of the shortage of board certified pathologists, is it permissible to permit either non-veterinarians or non-board certified veterinary pathologists to conduct necropsies? Is certification required for a pathologist to participate in a nonclinical laboratory study?

    The Agency recognizes the serious shortage of trained and certified pathologists as well as toxicologists. The GLPs require that personnel possess the appropriate combination of education, training and experience needed to do their jobs. Therefore, it is permissible to have non-veterinarians conduct necropsies provided their training and experience are adequate. The GLPs do not require board certification for either pathologists or toxicologists.

27. What does the agency consider to be the minimal acceptable educational requirements for someone appointed as "study director? "

    Due to the wide range of nonclinical laboratory studies and the numerous combinations of education, training and experience, which would be acceptable, the Agency did not specify minimal educational requirements for nonclinical laboratory study participants. The GLPs specify that the study director should have the appropriate mixture of education, training and experience to permit the performance of the assigned functions.

28. Will I, as the director rector of a contract pathology laboratory, be required to have a quality assurance unit and to store slides, blocks, wet tissues, etc. in the archives?

    The GLPs require that the quality assurance functions be performed. In your case, either you or the sponsor must have a quality assurance unit. Again, either you, the sponsor, or a separate commercial facility will have to store slides, blocks, wet tissues, etc., and the archives will have to specify the storage location.

SUBPART C
FACILITIES

58.41 GENERAL
58.43 ANIMAL CARE FACILITIES
58.45. ANIMAL SUPPLY FACILITIES
58.47 FACILITIES FOR HANDLING TEST AND CONTROL ARTICLES
58.49 LABORATORY OPERATION AREAS
58.51 SPECIMEN AND DATA STORAGE FACILITIES
58.53 ADMINISTRATIVE AND PERSONNEL FACILITIES

1. Would there be any criticism of a laboratory where animals of the same species, used concurrently in 6-8 short-term eye or dermal irritation studies, were housed in the same room, assuming there is sufficient spatial separation?

   No. This procedure would be acceptable provided that precautions were taken to prevent animal and experimental mix-ups and cross-contamination.

2. What is the relationship between the FDA and the USDA inspection of animal facilities?

   The USDA inspection is directed towards ensuring the humane care of animals used in research whereas the FDA inspection is directed towards ensuring the quality of data obtained from safety experiments that involve animals.

3. We feel that storage of test article - diet mixtures in animal rooms in well-labeled, vermin proof containers will lead to fewer errors than storage in a central common area. Is this permissible in light of section 58.47(b)?

   Yes. Section 58.47(b) requires separate areas for test article diet mixtures, which need not be a separate common area or a separate room. In the cited example, each animal room could have a separate area devoted to feed storage.

4. Is it necessary to provide space for the isolation of diseased animals if they are immediately removed from the study and sacrificed?

   No. The intent of the regulations is to ensure that diseased animals are handled in a manner that will not adversely impact on the nonclinical laboratory study.

5. Is it acceptable for a nonclinical laboratory to quarantine all newly arrived animals for the required period and then begin the study in the same area?

   Yes.

SUBPART D
EQUIPMENT

58.61 EQUIPMENT DESIGN
58.63 MAINTENANCE AND CALIBRATION OF EQUIPMENT

1. Regarding GLP required standard operating procedures for preventive maintenance, is it expected that detailed instructions be prepared for each piece of laboratory equipment? Can the standard operating procedures refer to an equipment manual for detailed instructions as appropriate?

   Specific standard operating procedures are required for each piece of equipment. These procedures can incorporate verbatim the instructions contained in the equipment manuals.

2. In order to calibrate a scale used to weigh large farm animals is it necessary to use a set of standard weights similar to those used for laboratory animal scales only much, much heavier?

   In this case, calibration and maintenance of a periodic nature can be performed by a manufacturer's representative and the records should reflect these operations. Additionally, calibration can be accomplished through use of secondary standards.

SUBPART E
TESTING FACILITIES OPERATION

58.81 STANDARD OPERATING PROCEDURES
58.83 REAGENTS AND SOLUTIONS
58.90 ANIMAL CARE

1. Is there a published tolerance regarding the amount of copper in water on the basis of species?

   The Agency is not aware of any.

2. With regard to section 58.90(c), does "separate" mean a separate air supply as well as space?

   Yes, insofar as it is required to ensure effective isolation of the disease.

3. There are many common reagents used in safety studies (e.g. glucose, sodium chloride, etc.). Do the GLPs intend that these reagents be labeled with storage conditions and expiration dates?

   Yes. It is of utmost importance that outdated and deteriorated reagents not be used in the study.

4. What are the environmental requirements for large animal (cattle/horses) safety studies?

   Guidance on this matter can be obtained by contacting the appropriate preclearance division within the Bureau of Veterinary Medicine.

5. How long do animal care records (cage cards, vendor information, etc.) need to be retained?

   These records should be retained in the archives for the terms specified in section 58.195.

6. Does approximate age of the test system need to be listed on the cage cards?

   No.

7. Why can't textbooks and manufacturer's literature be used as standard operating procedures?

   Textbooks and manufacturer's literature are not necessarily complete and it is highly unlikely that such materials could be used without modifications to more precisely fit

a laboratory's needs. These materials may be used, however, as supplements to and references for standard operating procedures.

8. In the absence of the "Guide for the Care of Laboratory Animals," what reference will FDA use in inspection of facilities for determining appropriate cage sizes, animal environment, animal facilities, veterinary care, and animal care practices?

   References to the guide and regulations promulgated by other agencies have been deleted from the final order on the GLPs. Nonetheless, these materials do provide guidance on the current state-of-the-art for animal care and they are helpful both to the laboratory and to the Agency in determining the adequacy of animal care practices.

9. Are expiration dates required on purchased chemicals and reagents present in the laboratory?

   Yes, expiration dates are required on such chemicals and reagents when they are used in a nonclinical laboratory study.

10. Are expiration dates required on prepared solutions made from purchased chemicals and reagents?

    Yes.

11. Are stability data required to substantiate the expiration dates of reagents and solutions?

    Not necessarily. It is sufficient to use scientific judgement coupled with literature documentation, manufacturer's literature or laboratory experience.

12. With respect to evaluating the effectiveness of reagents and solutions throughout their shelf life, what requirements are there on the certification of efficacy of the test reagents used to evaluate the effectiveness of the GLP reagents and solutions?

    Standard operating procedures for the analyses should provide such efficacy tests for reagents and solutions as the scientific literature, the manufacturer's literature, and the laboratory experience indicate are necessary.

13. What does the Agency expect in the area of analysis of feed and drinking water for known interfering contaminants?

    The GLPs require analysis for and control of contaminants known to be capable of interfering with the nonclinical laboratory study and which are reasonably expected to be present in the feed and water. Certain contaminants may affect study outcome by masking the effects of the test article, as was the case in recent toxicological studies

of pentachlorophenol and diethylstilbestrol. In these studies the feeds used as carriers of the test article were found to contain varying quantities of pentachlorophenol and estrogenic activity. These contaminants invalidated the studies by producing erratic results. The use of positive and negative controls in these studies was insufficient to compensate for the variability in the concentration of the contaminants.

To implement this provision of the GLPs, the study director and associated scientists should consider each study in the light of its length, the expected toxicological endpoints and pharmacological activity of the test article, the test system, the route of administration, and other relevant factors to determine what contaminants could reasonably be expected to interfere. These considerations coupled with scientific literature, experience and anticipated levels of contamination should be used to determine which contaminants should be controlled and analyzed.

It is unlikely that a blanket analysis conducted either by feed manufacturers or water authorities would be sufficient. These analyses would either provide data on contaminants which would not be expected to interfere or neglect to provide data for certain interfering contaminants.

For acute studies in which the test article dosage is sufficiently high, in most instances, to overcome any effects from feed or water contaminants, the analytical requirement would be minimized.

14. Study directors are frequently unfamiliar with certain aspects of their studies (e.g. chemical analyses, histopathology, etc.). Is it appropriate for the study director to authorize all deviations from standard operating procedures?

    Yes. As the focal point for study direction and conduct, the study director must be made aware of and react positively to any deviation from a standard operating procedure. Where necessary, a study director should consult with other scientists to determine the impact of a deviation on the study.

15. Is it required that the quality assurance unit test the reagents used in a nonclinical laboratory study?

    Whatever testing is required by section 58.83 of the GLPs for reagents and solutions may be accomplished by those organizational units that normally conduct such testing. It need not be done by the quality assurance unit.

16. May reagent grade chemicals be used in a study on the basis of label analysis declaration?

    Yes, provided that the reagent is labeled with an expiration date.

17. If animals do not have some form of unique identification actually attached to the animal, is identification using only cage cards appropriate? If the test system is housed in individual cages, which are uniquely identified, must each and every animal be identified?

    Section 58.90(d) requires that animals which are to be removed from their home cages or which are to be observed over a long period of time have appropriate identification. Therefore, identification using only cage cards is not sufficient in most cases and each animal should be identified.

SUBPART F
TEST AND CONTROL ARTICLES

58.105 TEST AND CONTROL ARTICLE CHARACTERIZATION
58.107 TEST AND CONTROL ARTICLE HANDLING
58.113 MIXTURES OF ARTICLES WITH CARRIERS

1. Are laboratories required to go beyond shelf storage of reserve samples of test article-carrier mixtures to whatever methods (e.g., cryogenic temperatures), regardless of cost that will maximize stability? Does the Agency expect stability studies to determine optimum storage conditions for each sample?

   No, heroic measures need not be taken. Storage conditions should be consistent with the knowledge of the stability of the mixture under conditions of use and reasonable so as not to permit accelerated decomposition.

2. What are the details of the Agency's reserve sample retention policy?

   With regard to reserve sample retention, the GLPs provide as follows:

   Reserve samples are to be retained from each batch of test and control article prepared in accord with section 58.105(a) for all nonclinical laboratory studies lasting more than 4 weeks. For the purposes of these sections, the 4-week period includes initial dosing to the final *in vivo* observations. Only sufficient sample need be retained to permit meaningful reanalysis. The samples need be retained either for the terms specified in section 58.195 or for the useful life of the sample (dependent on the stability or the quality of the sample) whichever is shorter. Storage conditions should be those commonly accepted as minimizing the deterioration of sample quality and need not require exhaustive study to determine those which maximize stability. All batches of test and control article mixtures are to be retained even if they are prepared daily.

3. For medical devices, how can stability be demonstrated any more effectively than by the continued functioning of a device within specifications during an *in vivo* nonclinical study?

   The stated procedure is acceptable.

4. The cost of chemical assay development and assay of dosage forms prior to conducting acute studies far exceeds the cost of doing the experiment. Will data confirming the weighing, mixing and administration of the test article be considered sufficient?

   No. The test article must be sufficiently characterized to ensure that the same article is used in any further studies.

5. Does FDA expect a firm to conduct long-term stability tests on test article-carrier mixtures, which are used within a day of preparation?

   The firm must determine the stability of the mixtures over the period of their use. The GLPs require retention of samples of all batches of test article-carrier mixtures for studies that last longer than 4 weeks. The regulations do not require stability studies on such samples. Samples placed in storage may be analyzed periodically to determine their useful storage life.

6. Am I correct in assuming that the chemical testing done by the sponsor to characterize the test article is not covered by the GLPs when the test article is subsequently submitted to a contract laboratory as a blind sample for safety testing?

   The GLPs do not cover the basic exploratory chemical tests done to derive the specifications of the test article. They do cover those chemical tests done on discrete batches of test article to determine identity, strength, purity and composition.

7. Does the phrase "mixtures of articles and carriers" also refer to solutions and suspensions, e.g., a solution of a test article in distilled water?

   Yes.

8. For acute studies, is it necessary for the laboratory to analyze each batch of test article-carrier mixture prior to dosing the test system?

   No. Uniformity of the mixture must be known and periodic batch analyses need to be done.

9. Will dialogues such as this and recent inspectional experience bring about substantive changes in the final regulations through FDA initiated proposed amendments? What changes are anticipated in the reserve sample retention requirements?

   The Agency does not believe the initiative to change the GLPs rests with FDA. Petitions for change may be submitted to the Agency in accord with the 21 CFR 10.30. As was mentioned at the meeting, the Agency recognizes that the reserve sample retention requirements are extensive and expensive and a petition for change would be considered.

10. What guidelines can be used by a laboratory or sponsor in deciding how frequently concentration analyses should be made?

    The Agency has not established guidelines with regard to the frequency of periodic reanalysis of test article-carrier mixtures. Enough batches should be analyzed to

assure that the test systems are being exposed to the quantities of test article in the specified protocol.

11. How long must one retain samples of feed used in nonclinical laboratory studies and should they be frozen?

    The sample retention period differs for the various regulated products and the periods are listed in section 58.195. Feed samples need not be frozen for storage.

12. What is the definition of carrier?

    Carrier is the material with which the test article is mixed for administration to the test system. It can be feed, water, solvents and excipients depending on dosage form and route of administration.

13. Once stability of a given concentration of a test article-carrier mixture is substantiated, is it necessary to establish a stability profile for each batch at that concentration?

    No. Stability need be determined only on a single batch of test article-carrier mixture; however, periodic reanalysis to determine concentration must be done.

14. In the course of a 14-C tissue residue study in the target animal, is it necessary to retain:

    a. a sample of the 14-C labeled drug,
    b. samples of the diet fed control and experimental animals,
    c. samples of urine and feces after completion of the analyses,
    d. samples of collected tissues after completion of the analyses,
    e. if they must be retained, for how long?
    f. is similar sample retention necessary when doing "cold" tissue residue studies in target animals?

    All samples listed in a - d and f above should be retained for the term listed in section 58.195.

15. If a battery of different tests on a substance is being conducted by different contractors, is it necessary to run replicate stability analyses from each and every contractor especially when long-term stability has been documented for the substance?

    No. Once stability has been determined in accord with good science, it is not necessary to continually replicate the stability determination.

SUBPART G
PROTOCOL FOR AND CONDUCT OF A NONCLINICAL LABORATORY STUDY

58.120 PROTOCOL
58.130 CONDUCT OF A NONCLINICAL LABORATORY STUDY

1. In as much as only wet tissues, blocks and slides are necessary to reconstruct the histopathologic aspects of a study by a third party, are written notes, tapes, etc. of the histopathologist's thought process in arriving at a final report legitimately considered "raw data" in the presence of a signed and dated final report? Does the Agency have the right to inspect the written notes from the pathologist?

   Raw data in this case, refers only to the signed and dated final report of the pathologist. Agency investigators may wish to examine the interim notes and reports in an attempt to reconstruct the study but not to second-guess the scientific process used to arrive at the final report. The GLPs do not require that these interim reports and notes be retained.

2. What is considered to be raw data in computer systems when the data is generated from dictated results?

   Transcribed dictation, which has been proofread and corrected for typographical -and transcription errors, is raw data.

3. Do the GLPs require that the protocol be amended to reflect the actual starting date of the study?

   Yes, this is a critical piece of information, which should be supplied by way of a formal protocol amendment.

4. It is said that raw data may be any verified exact copy of the original data. In a computerized data system where data is put directly on disc thence to tape, what documentation of the program performing this transfer is required to assure that the tape copy is exact?

   The standard operating procedures, which cover computer operations, should describe the computer program and the procedure used to assure the production of an exact tape copy.

5. If reformatting of data is done as part of the transfer described in question 4 above, is the new file not raw data even if all data is transferred intact although in a different organization?

   The Agency can not precisely answer this question without further details of the new data format.

6. Are initials and dates on data printouts (e.g., scintillation counters, gas chromatographs), when these printouts include standards, sufficient documentation for standardization?

   Yes.

7. Is there a time limit for submission of the final report of a nonclinical laboratory study after its conclusion?

   Generally no. On occasion, for marketed products, the Agency may establish time frames for study conduct. Of course alarming findings on marketed products should be reported as soon as possible.

8. Is it permissible to list changes in a final report on a page, which is appended, to the original final report?

   Yes.

9. Does "studies in progress on June 20, 1979" refer to the phase of dosing of the test system or the phase post-dosing but not yet reported?

   The quotation pertains to all studies for which the final report has not yet been completed. Included are all post-dosing phases.

10. The final report requires a list of participants. Should this include technicians as well as people who perform support functions?

    The final report should include the name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel involved in the study.

11. When an analysis protocol is developed for the first time by using standard scientific technique, who shall validate the protocol?

    The Agency does not *per se* validate protocols. Persons developing new protocols may submit them to the responsible bureau for review and comment prior to initiating a nonclinical laboratory study.

12. Why is the signature of the sponsor required on a protocol for routine acute testing when these procedures are published and sufficiently standardized by the industry? Would written standard operating procedures of the testing facility be sufficient to replace the protocol without the sponsor signature?

One of the testing deficiencies found in the early Agency investigations of nonclinical studies was protocol changes that were made without informing the sponsor. The changes prejudiced the validity of the studies. Accordingly, the GLPs require that each study have a specific protocol, which is attested to by the sponsor.

13. The identity of the individual collecting data entered into a computer can be recorded via the use of a code known only to the individual but directly identifying the individual; similarly the identity of the individuals witnessing or reviewing the data can be recorded. Is this acceptable?

    Yes, this procedure is acceptable. The key to the code must be made available to Agency investigators. Do note, however, the final GLPs do not require that data entries need be witnessed by a second person.

14. Does the following proposal on data entry to computer files satisfy the GLP intent?

    > Data is entered through keyboard commands and stored in a "temporary" computer file with accompanying date, time, and analyst codes. The analyst may be technician level personnel. At the conclusion of a set of observations, no more than one day's worth, the data in the "temporary file" is reviewed by a scientist (this person may or may not be the same person who entered the original data) and "corrected" for any typing or entry errors. When it is determined that the data are correct, the data are transferred to a "permanent" computer file. Only authorized personnel may make changes to the "permanent" file.
    >
    > No audit trail is kept for changes to "temporary" file. All changes to permanent file are recorded in a change file with appropriate data, personnel code, and comments regarding reason for change and original entry.

    No. This method would permit unauthorized tampering with the temporary file before the raw data are transferred to the permanent file.

15. When should a protocol amendment issue? Should it be as soon as possible or could a list of all deviations from a protocol be prepared at the end of the study?

    If the deviation from the protocol is intended to be permanent, the protocol should be amended as soon as possible. If the deviation is an error, it should be promptly corrected and noted in the raw data.

16. Section 58.120 describes a sixteen-part protocol and section 58.185 describes a fourteen part final report. Must all of these be included in protocols and reports for LD 50's and other short-term tests?

    Yes.

17. Is a protocol required for routine research and experimentation?

    Protocols are required for all studies covered by the GLPs.

18. If all raw data are not required in a final report, does this mean, for example, that weekly body weight or food intake averages can be in a report without the individual animal data?

    The data appearing in a final report depends on the type of study and the kind of regulated product. Specific advice can be obtained by contacting the Agency bureau, which has responsibility for the regulated product.

19. If a compound or formula is proprietary, must the final report describe its detailed composition or chemical structure?

    If the proprietary material is a commercially available article to be used as a control, the final report need only describe the trade or chemical name, the source and the manufacturer's batch number.

20. How does the requirement for "approval" of protocols apply to "in house" studies which are' conducted in the laboratories of the actual "sponsor?" Who approves? What is an "approved" protocol?

    The word "approved" was retained in the final order to emphasize that a sponsor should have a mechanism for evaluation and approval of initial protocols and all amendments. The specifics of the mechanism can vary but a formal mechanism should be in place.

21. Must the protocol contain both the name and the code number of the test article?

    No, either designation is acceptable.

22. Section 58.120 states that the protocol shall contain the records to be maintained. Is this intended as a detailed list of each data form to be generated?

    No, in this case generalized statements would be satisfactory.

23. How much raw data must be entered into notebooks when performing well-documented routine tests?

    Basically, the GLPs define raw data as the immediate results of original observations. All such immediate results must be entered.

24. What is meant by the statement in section 58.120(a)(12), which pertains to the method by which the degree of absorption of the test and control articles by the test system will be determined?

    The GLPs do not mandate that absorption studies need be done, or which kind of study is satisfactory. The GLPs do require, however, that the protocol describe the method used if one is necessary to achieve the study objectives.

25. Please clarify the issue of having to provide reasons for all corrections to data entries. It seems unreasonable to require reasons for "obvious" error corrections such as misspell ings, transposed numbers, and wrong year early in a calendar year.

    It must be remembered that "raw data" is basically the results of original observations. Thus, the wrong year is not raw data and can be easily corrected. Misspellings may or may not be raw data whereas in all probability numbers are raw data. The Agency believes that it is sometimes difficult for a second party, such as the personnel in your quality assurance unit, to distinguish "obvious" errors. Consequently, the Agency insists that all corrections to raw data entries be justified.

26. How and to what extent is the selection of the test system to be justified in the protocol?

    Usually, the test system is selected after consideration of the state-of-the-art of toxicology testing in the area of interest. The protocol need not contain extensive justification.

27. Are we expected to label all specimens (e.g. serum, blood, urine, tissue slides) with their exact nature?

    Yes. Such information is useful in preventing mix-ups.

28. Why does "test system, study, nature and date of collection" have to be located on a specimen container? Can such information be coded?

    Specimen refers to any material derived from a test system for examination or analysis. Consequently, blood, tissues, urine, feces, etc. are considered to be specimens whose containers must carry the required label information. Such information will help preclude mix-ups in the subsequent handling of the specimens. Accession numbers or code numbers can be used for samples of specimens, which are subjected to further analysis. For example, in histopathology the excised fixed tissue is a specimen, which must carry all the label information. However, the blocks and slides prepared from that tissue could be identified by accession numbers. Similarly, in tissue residue analysis, the excised tissue is a specimen; whereas, tissue samples, which are homogenized and otherwise prepared for further analysis, are not specimens and need not carry full labeling.

SUBPART J
RECORDS AND REPORTS

58.185 REPORTING OF NONCLINICAL LABORATORY STUDY RESULTS
58.190 STORAGE AND RETRIEVAL OF RECORDS AND DATA
58.195 RETENTION OF RECORDS

1. What types of storage conditions are required for the storage of retained specimens?

   The Agency has not developed guidelines for storage conditions. The Agency does not expect heroic measures to be used, but conditions should be reasonable in light of the nature of the specimen. Storage conditions, which foster accelerated deterioration, should be avoided.

2. In section 58.185, it is stated that test and control article identification and characterization must appear in the final report signed by the study director. However, if the study director is affiliated with a contract laboratory, he/she has no need to know such details of a proprietary test article. Do you agree that such information can be appended to the final report by the sponsor rather than be provided by the study director?

   Yes.

3. Is the storage of archival material (tissues, slides, raw data) the responsibility of the testing laboratory or can this responsibility be assigned to the sponsor of the study?

   The GLPs permit these materials to be stored in the archives of either the testing laboratory or the sponsor. If they are stored in the sponsor's archives, the archives of the testing laboratory must identify the storage location.

4. If a sponsor agrees to characterize and store test articles submitted for study to a contractor, must the contractor also verify the characterization and provide storage for the test articles?

   No, but the contractor must identify the storage location.

5. What is the "completion date" of a nonclinical laboratory study?

   The completion date is the date that the study director signs the final report. Some discretion must be used however, since the protocol calls for a proposed "completion date." In this case, it would be adequate for the protocol to list a completion date for the in vivo phase and qualify it as such.

6. With respect to archival material, what is required to be listed as the date of the study?

   The study date would be the same as the completion date of the study.

7. Do all studies on a test article need to be submitted in support of an application for a research or marketing permit?

   All studies need be submitted, however, not all studies need be conducted in accord with the GLPs. The conforming amendments provide that a statement be included in the submission which identifies which studies have not been conducted in compliance with the GLPs and the extent of the non-compliance.

8. What should be included in the signed and dated reports of the individual scientists participating in the study?

   The final report prepared by the study director should have appended to it all reports written by other participating scientists. These reports should contain sufficient detail to enable the study director to write a final report, which reflects the results of the study.

SUBPART K
DISQUALIFICATION OF TESTING FACILITIES

58.200 PURPOSES
58.202 GROUNDS FOR DISQUALIFICATION
58.204 NOTICE OF AND OPPORTUNITY FOR HEARING ON PROPOSED DISQUALIFICATION
58.206 FINAL ORDER ON DISQUALIFICATION
58.210 ACTIONS UPON DISQUALIFICATION
58.213 PUBLIC DISCLOSURE OF INFORMATION REGARDING DISQUALIFICATION
58.215 ALTERNATIVE OR ADDITIONAL ACTIONS TO DISQUALIFICATION
58.217 SUSPENSION OR TERMINATION OF A TESTING FACILITY BY A SPONSOR
58.219 REINSTATEMENT OF A DISQUALIFIED TESTING FACILITY

ENFORCEMENT STRATEGY

1. What can FDA do to force a laboratory to take corrective actions to achieve compliance with the GLPs? Are warnings given to the laboratory?

   FDA has a number of regulatory sanctions, which can be brought to bear on a violative firm in order to, bring about compliance with the law. These include rejection of studies, withdrawal of approval of marketed products if such products are supported by defective studies, prosecution and, after June 20, 1979, disqualification of the laboratory. FDA's present GLP enforcement policy is to provide adequate warning and to afford a reasonable opportunity to take corrective action.

   Disqualifying a laboratory on the basis of failing to comply with one or more provisions of the GLPs raises the question of whether all violations are considered-equally, are weighted, or are evaluated scientifically to consider the impact on the outcome of the study.

   A laboratory will not be considered for disqualification unless all of the following criteria are met:

   a. failure to comply with one or more provisions of the GLPs;
   b. the noncompliance adversely affected the validity of the studies;
   c. other lesser regulatory actions (warnings, rejection of individual studies) have not or will not be adequate to achieve compliance with the GLPs.

   The violations of the various provisions of the GLPs are evaluated to assess their impact on the validity of the studies. It is impossible to assign weights to the various

provisions of the GLPs. Noncompliance with the various provisions must be evaluated in the context of the entire laboratory operation and the kinds of studies being performed. Thus, a violation of a specific provision may be critical for one laboratory doing long-term studies and not for another laboratory engaged in short term studies.

3. If a laboratory is disqualified, how long does the disqualification last? Under what conditions does reinstatement occur?

   The disqualification will last until the laboratory submits in writing to the Commissioner, reasons for reinstatement including a detailed description of the corrective actions it has taken to assure that the violations which led to disqualification will not recur. Reinstatement will depend upon one or more inspections which show that the laboratory is in compliance with GLPs.

4. Paragraph 231 of the preamble to the GLPs states: "The order of disqualification creates a rebuttable presumption that all studies previously conducted by the facility are unacceptable. Paragraph 226 states: "Studies conducted at facilities that are in substantial compliance will be presumed to be valid." Can we presume that studies conducted during a period when a lab is found to be substantially in compliance will be accepted by FDA as valid even if the laboratory is disqualified at a later date?

   Yes, unless FDA develops information to the contrary.

5. If a contract laboratory is disqualified because of a study performed for one sponsor, what effect does this have on other studies performed for other sponsors? What about studies underway at the time of disqualification?

   FDA will not disqualify a laboratory on the basis of one invalid study. Disqualification is viewed as a most serious regulatory sanction by FDA and will only be imposed when the facts demonstrate that the laboratory is incapable of producing valid scientific data and will not take adequate corrective measures. In the event a laboratory is disqualified, all studies performed by the laboratory, including those in progress are presumed to be unacceptable unless the sponsors of those studies can establish, to the satisfaction of FDA, that the studies were not affected by the circumstances that led to the disqualification.

6. What steps must be taken by FDA prior to removal of a product from the market because of a rejected study which was pivotal to the assessment of safety?

   If rejection of a study results in insufficient scientific data being available to support a decision on safety for a marketed product, FDA will initiate formal proceedings to withdraw the marketing approval of that product. These proceedings, for drugs, begin with a notice published in the FEDERAL REGISTER of FDA's proposal to withdraw approval setting forth the basis for the proposed action and affording

affected parties an opportunity for a public hearing on the matter. If a hearing is requested, affected parties will have the opportunity to present additional facts at the hearing for the Agency to consider The Commissioner's decision to withdraw or to continue the approval is based on the facts brought out at the hearing.

ENFORCEMENT STRATEGY

GENERAL POLICY

1. What is the regulatory basis for conducting GLP inspections? It would seem that by making the GLPs regulations instead of guidelines, that the attorneys and accountants are managing the studies. How does that produce good science?

   The GLP regulations are process-oriented; they are designed to assure that the data collected in a nonclinical laboratory study are valid and accurately reflect the responses of the test system. The GLP inspections are necessary to assess the degree of compliance with the GLPs. The science of a study depends on the appropriateness of the design selected to answer the questions raised in the use of the test article as well as the soundness of the conclusions drawn from the data collected in the study. The assessment of the scientific merit of a study is made by scientists.

2. Does FDA have the authority to audit an ongoing study of a product for which an application for a research or marketing permit has not yet been submitted to FDA?

   A distinction needs to be made between an audit of a study and a GLP inspection. An audit involves a comparison of raw data with completed reports to identify errors and discrepancies. A GLP inspection involves an assessment of the procedures used to carry out the study and to record and store the data. FDA audits only studies, which have or are intended to be submitted to the Agency. The FDA will, however, look at on-going studies whether or not they involve FDA regulated products for purposes of documenting the laboratory's adherence to GLPs; such an inspection does not, however, constitute a data audit of the study rather it is an audit of the "process."

3. What happens when a laboratory refuses to permit an inspection of its facilities?

   If the laboratory is actively conducting studies on investigational new drugs, investigational new animal drugs, or investigational devices, refusal to permit inspection is a violation of section 301(e) or (f) of the Act and the Agency will take whatever action is required to compel inspection.

   Where the Agency has reason to believe that the laboratory is in fact conducting nonclinical laboratory studies, a letter will issue to the laboratory stating that FDA will not accept any future studies performed by that laboratory in support of a research or marketing application. If the laboratory has not, or is not testing an FDA regulated product, it is also advised to contact the local FDA district office to arrange for an inspection should they anticipate engaging in such safety testing.

4. What happens if in the course of an inspection of a contract laboratory, the sponsor of the study selected for GLP inspection refuses to permit access to the study records?

   The FDA investigator will select another study and proceed with the inspection. If the study originally selected for inspection involved an FDA regulated product, the Agency will pursue the matter directly with the sponsor.

5. If GLP regulations are not retroactive, will FDA audit pre-June 1979 studies? If so, will FDA investigators list non-conformance with GLPs on the FD-483 Notice of Observations associated with those studies?

   FDA will continue to audit pre-June 1979 studies for purposes of assessing not only the quality of a particular study, but also the general performance of the laboratory prior to the time when GLP regulations were first proposed in November 1976. This is necessary because many of the marketing applications pending before the Agency contain studies performed prior to 1976.

   While deviations from the GLPs will be noted in the FD-483 associated with these studies, the Agency will use this information only to make a judgment regarding the scientific acceptability of those studies and will not use the deviations to initiate regulatory action against the laboratory. After the June 1979 effective date, however, deviations from the GLPs could result in regulatory action against both the studies and the laboratories.

6. Will the GLPs apply to a study, which has been completed prior to the June 20, 1979, effective date for which a final report will not be prepared until after?

   The GLP regulations became effective June 20, 1979, and those portions of studies underway, as of that date, even if only the final report, became subject to the regulations at that time.

7. Will a laboratory engaged in testing an FDA-regulated product be subject to a GLP inspection if a research or marketing application has not been submitted to the Agency, e.g., a new company developing its first products?

   Generally speaking, FDA inspects only those laboratories, which have conducted studies submitted to the Agency. FDA strongly advises any laboratory which intends to engage in the safety testing of a regulated product, and which has not been previously inspected, to contact the local FDA district office and request a GLP inspection.

8. Will FDA accept data from a study not conducted in accordance with GLPs for regulatory purposes?

Even though a study has not been conducted totally in accordance with GLPs, FDA may accept the data from such a study if it can be demonstrated that the areas of non-compliance have not compromised the validity of that study. As a special corollary to this policy, FDA will take note of positive findings of toxicity in a study even though that study was not conducted in compliance with GLPs. While a technically bad study can never establish absence of a safety risk, it may establish the presence of an unsuspected hazard or untoward effect.

9. Where can the Inflationary Impact Assessment Report of the GLPs be obtained?

   By writing to the: Hearing Clerk
   Food and Drug Administration
   5600 Fishers Lane
   Rockville, MD 20857

10. How does FDA protect the confidentiality of valuable commercial or trade secret information given to an investigator during a GLP inspection?

    FDA employees are required by statute to protect the confidentiality of any trade secret or confidential commercial information which they may acquire in the performance of their duties. Thus any trade secret information which an FDA investigator may receive from a laboratory being inspected is exempt from public disclosure. Whenever the FDA receives a Freedom of Information Act request for a copy of the laboratory inspection report, all information which falls under the definition of trade secret or confidential commercial information will be purged from the report before it's released.

    From a practical standpoint, there is a "gray area." of information, which may or may not be privileged information. FDA personnel will make every effort to determine whether the rules of confidentiality apply in such cases. The final decision, however, will be FDA's.

11. Will FDA review non-GLP studies (range-finding, exploratory studies) in the course of conducting GLP inspections of studies intended to be submitted to the Agency? This is of particular concern in protecting proprietary research data. Will there be an opportunity for the inspected firm to do an FOI review before the final inspection report is written?

    FDA may review on-going non-GLP studies as described in question 23 on Subpart A and question 11 under "Inspections."

    The inspected firm may not review a draft inspection report for purposes of identifying what should not be released under FOI. Even if the Agency permitted this, which it does not, the fact that the report was made available to someone outside

the Agency would immediately make that draft document available for public disclosure under the provisions of the FOI regulations.

12. Will foreign laboratories be inspected to determine their compliance with GLPs?

    Foreign laboratories, which conduct studies submitted to the Agency, will be inspected and held accountable to the same GLP requirements as U.S. laboratories. While FDA has no authority to inspect foreign labs, the Agency has adopted the policy of not accepting data from any laboratory (domestic or foreign) which refuses to permit an inspection of its facilities.

13. What accords have been made with foreign countries regarding GLPs and inspections?

    FDA has signed a Memorandum of Understanding with Canada and Sweden, which commit both countries to establish GLPs and an inspection system. Discussions, which may lead to similar accords, have been held with Great Britain and Switzerland. Informal expressions of interest have been received from other countries. The long-range objective of these bilateral agreements is reciprocal recognition of each country's GLP program.

14. Has FDA inspected its own animal research facilities for compliance with GLPs? Other Federal laboratories?

    Yes. To date, FDA has completed GLP inspections of all its animal research facilities and is taking steps to bring all its laboratories into compliance. FDA has also established contacts with the NIH, DOD and USDA for purposes of scheduling inspections of laboratories performing safety studies intended to be submitted to the Agency.

15. Has FDA established liaisons with other Federal agencies regarding the GLP program?

    Yes, liaisons have also been established with CPSC, EPA, and OSHA for purposes of furthering the objectives of the GLP program, scheduling inspections of Federal laboratories and sharing information resulting from the FDA program.

INSPECTIONS

1. Is it possible that an FDA investigator may take exception to a firm's definition of regulated and nonregulated laboratory studies? If such a difference of classification arises for a given study, how would you resolve the conflict with the FDA?

   Yes, it is possible. The testing facility may appeal any differences it has with the investigator first to the FDA district office and, if this is not satisfactory to FDA headquarters.

2. What is the estimated number of laboratories being inspected by FDA?

   FDA's inventory of laboratories subject to GLPs includes approximately 380 domestic laboratories and 110 foreign laboratories. The laboratories include sponsor laboratories, commercial contract laboratories and university laboratories.

3. Will the inspectional training course at the National Center for Toxicological Research be open to industry and academia?

   No. The training of industry and academic personnel to enable them to properly perform their duties is the responsibility of their employers. However, FDA is prepared to participate in any training courses, which may be offered by industry associations or the academic community to the extent that resources will allow.

4. If the GLPs are Phase I of Bioresearch Monitoring, what other phases are anticipated by FDA?

   Other phases include new regulations on obligations of sponsors and monitors of clinical investigations, obligations of clinical investigators, and obligations of institutional review boards. Note that these regulations are directed towards efficacy data and the protection of human subjects whereas the GLPs are directed towards safety data.

5. Who makes the decision on whether or not a headquarters scientist participates in a GLP inspection? Why can't we have a headquarters scientist on each inspection?

   The scheduling bureau makes the decision. During the past two years, headquarters scientists have participated in about half of all GLP inspections and, with rare exception, the Bureau of Biologics assigns a headquarters scientist to each GLP inspection. Resources do not permit more extensive participation.

6. How are laboratories selected for inspection?

   Laboratories are selected for inspection by bureaus within FDA. The criteria for selection are actual or potential involvement in studies associated with products

regulated by FDA. Inspections will involve a specific study submitted to a bureau or a study selected from the firm's master list which is of interest to FDA.

7. How often can a laboratory expect to be inspected?

   Routine surveillance inspections will occur at least once every two years or more frequently depending upon findings of previous inspections. However, more frequent inspections may occur when an audit of a specific study submitted to FDA or EPA in support of a marketing application is required.

   Either type of inspection can result in more frequent visits if serious adverse findings are reported. These latter visits are considered compliance or follow-up inspections and are carried out to determine if correction of previous violative conditions have been made.

8. Will laboratories be notified in advance of an inspection?

   Because of the comments received during the conferences and the experiences to date with this program, laboratories will generally be notified prior to inspection. However, compliance or special investigation inspections may not follow this procedure.

9. Can a laboratory postpone an inspection?

   A facility may at the time of initial FDA contact request a postponement. Such a postponement may occur when personnel responsible for the conduct of the study to be audited will be unavailable at the anticipated inspection date. FDA expects to be reasonable in arranging for an inspection date. Unreasonable delays in scheduling the inspection will however be viewed by FDA as a refusal to permit an inspection.

10. Can a laboratory request an inspection? How?

    A facility may request an inspection from either the local FDA district office or from FDA headquarters. However, an inspection will be initiated only with headquarters concurrence. Consideration will be given to the work schedules under which district management is operating.

11. If a laboratory is not performing a study on an FDA regulated product at the time the investigator arrives, will the inspection still be carried out?

    Routinely, GLP inspections are not scheduled unless the Agency has received a final report on a regulated product or has received submitted protocols, interim study reports, or knows that a study on a regulated product is underway. In the case of a laboratory that is not currently performing a study on a regulated product the laboratory will be asked to consent to an inspection. The FDA investigator will

utilize an ongoing study, even though it is not associated with an FDA regulated product, to document the laboratory's compliance with GLPs. In such cases, the study will not be audited in terms of validating the raw data, and specifics of the study will not be included in the inspection report.

12. Will inspections cover other areas such as chemistry, physical testing, metallurgy, etc.?

    To the extent that the protocol of a nonclinical laboratory study requires tests in the field of metallurgy, clinical chemistry, etc., we will examine and evaluate adherence to test specifications or protocol requirements.

13. Are firms notified of specific studies to be audited? Will sufficient time be allowed to seek authorization from the sponsor of the study to disclose the data to the FDA investigator? What happens if the sponsor of the study refuses to authorize the laboratory to disclose the records?

    As stated with respect to prior notification of inspection, where FDA has an interest in auditing a study, ample time generally will be provided for the facility to seek authorization from the sponsor to disclose the data. In some cases, FDA investigators may begin inspecting the physical layout of the facilities while authorization to release the study records is being obtained. If the sponsor refuses to authorize disclosure of the records to the investigator, FDA will pursue the matter directly with the sponsor.

14. Can FDA investigators ask for records to which they are not legally entitled; can they engage in "fishing expeditions?"

    It is not FDA policy to request documents during an inspection to which the Agency is not legally entitled. On occasion, the Agency may request such documents when pursuing an audit trail of a possible violation. Under these circumstances, it is the laboratory's prerogative to cooperate or refuse without fear of reprisal. The requests should be specific and pertinent to the inspection. The Agency discourages investigators from making vague requests to see documents with no specific purpose in mind.

15. Should the Form-FD-483, Notice of Observations issued by the FDA investigator reflect current practices only; and should it include practices that were corrected during the course of the inspection?

    The FD-483 can include historical practices, which may have affected the scientific validity of the nonclinical study in question even though subsequent correction may have occurred. Any corrective action taken by the facility will be noted by the investigator in the establishment inspection report.

16. What should a laboratory do when there is disagreement between the laboratory and the FDA investigator regarding the findings reflected in the FD-483 Notice of Observations?

    At time of the observation, the management should discuss any differing opinions and attempt to clarify the investigator's perceptions or observations. The management may also, at the conclusion of the inspection, offer to explain what the management considers to be erroneous 483 observations. Should the matter in question remain unresolved, a written objection should be sent to the local FDA district director or a meeting with district personnel should be requested to attempt to resolve the issue.

17. What is the procedure for correcting errors in the FDA investigator's inspection report? Such errors can be damaging to the laboratories since the reports are ultimately available through FOI.

    If in fact an error is made in an investigator's report, the matter should be immediately brought to the attention of FDA district management. If district management agrees with the complaint, the report will be amended and amended reports will be sent to all outside persons who may have received the erroneous report. It should be stressed, however, that the time to change what a facility believes is an erroneous conclusion is when the FD-483 is discussed with laboratory management because as soon as the FD-483 is presented to management, it becomes available for public disclosure.

18. Does refusal to allow the FDA investigator access to certain information, which the laboratory sincerely believes is not subject to FDA jurisdiction, constitute a refusal of inspection? How can a disagreement of this kind be resolved?

    Refusal to permit access to records which are associated with a study being audited or which preclude a judgement being made regarding compliance with GLPs, is considered a refusal of inspection with certain ensuing consequences. However, a facility may legitimately question FDA authority to review certain documents. Such objections and the reasons therefore, should be presented in writing or by telephone to the FDA district office management where the investigator is based. Each case will be individually reviewed both in the field and, if necessary at headquarters and a decision will be communicated to the inspected facility.

19. Will inspections and audits of foreign laboratories be carried out? Who pays for these inspections?

    Inspections are being conducted of foreign facilities, which have engaged in nonclinical studies, which have been submitted to FDA in support of a marketing permit. FDA pays for travel and other expenses associated with such inspections.

20. In order for foreign laboratories to comply with the GLPs, do protocols, standard operating procedures, records, etc. have to be in English? Do FDA investigators bring interpreters with them to review records and data?

    Submissions to FDA in support of a marketing application for a FDA regulated product must be in English. Review of source documents at the site of the foreign facility may necessitate review of documents written in the language of the country of origin. FDA does not employ interpreters to accompany investigators on foreign inspections. It has been our experience that persons associated with the laboratory are normally fluent in the English language.

21. What kind of training does an FDA investigator have which qualifies him/her to conduct a GLP inspection or data audit? Does the investigator draw conclusions from his observations regarding the competence of the laboratory or quality of the studies?

    Along with education in one of the natural or physical sciences, the individuals selected to conduct GLP inspections generally have had considerable experience inspecting facilities involved in drug manufacturing, biologics production, medical device assembly, food processing, and a range of other operations on products regulated by the Agency. In addition, the investigators conducting nonclinical laboratory inspections (GLPs) have undergone intensive training in the normal operating procedures of nonclinical testing facilities. This training which includes a full review of the Agency's policies and of the GLP regulations National Center for Toxicological Research accomplished at FDA's National located in Pine Bluff, Arkansas. Field investigators are encouraged to contact any resource within the Agency, i.e., scientists and other personnel of the various bureaus to resolve scientific questions that may arise during an inspection. Bureau scientists and not the investigators, draw conclusions regarding the competence of the laboratory of the quality of the study

22. Does a laboratory manager have the right to ask for the FDA investigator's educational and experience qualifications prior to a GLP inspection?

    Yes, questions regarding the formal training, educational experience, and on-the-job training of an individual investigator may be addressed to the investigator prior to a GLP inspection.

23. What can a laboratory manager do when he encounters an FDA investigator who is overly antagonistic or uncertain as to what he is looking for?

    The Agency makes every effort to promote a professional attitude in its investigators including special training and selection of investigators for this program. However, if in the judgement of the laboratory manager there is a question as to the qualifications

or attitude of the investigator, the local FDA district office director should be contacted.

24. What assurance does a firm have that confidential or trade secret information given to the FDA investigator will be safeguarded by the Agency? What happens when an FOI request for the inspection report is received by FDA?

    Section 301(j) of the Food, Drug, and Cosmetic Act prohibits any employee from revealing for his/her advantage any information obtained in the course of carrying out his/her duties. Trade secrets and confidential commercial information are deleted from documents before they are released under FOI. Inspected firms may help by identifying information, which they consider to be confidential when it is given to the investigator. FDA will however, exercise its own judgment, in accordance with its FOI regulations as to whether such information may properly be classified as confidential.

25. How can copies of inspection reports be obtained under FOI?

    Inspection reports may be obtained by making a request under FOI to:
    Freedom of Information Staff, HFI-35
    U.S. Food and Drug Administration
    5600 Fishers Lane
    Rockville, Maryland 20857